It has been suggested that the presence of a strabismus in some of these cases would indicate that the nystagmus, under such conditions, at least, was the primary factor, but while the strabismus may indicate a palsy of one of the eye muscles nystagmus does not follow palsy of the eye muscles under other conditions.

A STUDY OF A CASE OF SPLENOMYELOGENOUS LEUKÆMIA.

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(From the medical service of Dr. Wainwright.)

The subject of this study was previously under the care of Dr. J. Emmet O'Brien, of Scranton, and Dr. Thompson, of Carbondale, to both of whom we are indebted for notes of his former history.

The patient stated that about six years before admission to the hospital he had a severe attack of abdominal pain, with vomiting and diarrhœa. He said that this illness was similar to his subsequent ones. He was given arsenic at the time, and made a good recovery, and was apparently in good health until late in the year 1902, except for a time in 1901, when he was bothered by a pain in the splenic area.

About October, 1902, he began to suffer again with "bloating" and with alternate constipation and diarrhœa. Dr. O'Brien first saw him on December 11, 1902. He found the spleen much enlarged. A record of the blood count was not kept, but it is known that the leukocytes were much increased in number, and smears showed the picture of a leukæmia of the splenomyelogenous type. Fowler's solution in increasing doses was prescribed. On January 3d the patient returned much improved, and the splenic tumor was not palpable. On January 28th the spleen could again be felt, and the leukocytes were still numerous. His general condition, however, seemed to be improved. He was last seen by Dr. O'Brien on March 24, 1903.

From March, 1902, until his admission to the hospital he was seen a few times by Dr. Thompson, who was called chiefly for gastrointestinal trouble. One of these attacks yielded to small doses of calomel daily. At another time he was again given arsenic, with benefit.

On the whole, during this period his condition was fairly good, He seems to have been troubled only by the attacks of diarrhœa, and he kept very steadily at his active duties as inside foreman of a coal mine until March 31, 1904.

The patient was admitted to the Moses Taylor Hospital on April 14, 1904.

Family History. Father died of miners' asthma[1] at the age of sixty-six years. Mother well at sixty-eight. Grandparents died of old age. Has one sister, aged forty-six years, and one brother, aged forty years. Both have always been well. One brother died of violence at the age of twenty-six years. He has been married twenty-one years. Wife is well. He has seven living children, all of whom are well. Three other children died in infancy of convulsions, diphtheria, and enteritis, respectively.

Personal History. He is forty-one years old. Was born in Wales. Came to this country when two years old. At ten he started to work in a coal breaker. At eleven he began to work inside the mines as a driver boy. He was for many years a miner, and for the last fifteen years has been inside foreman. He has worked continuously inside the mines for thirty years.

He has used alcohol and tobacco only in moderation, and denies venereal infection. There is no history of malaria.

Present Illness. In addition to the notes above he stated that while he did not give up work until two weeks before admission he had been gradually growing weaker for the past seven months, His only complaints have been a feeling of tightness in the epigastrium, "swelling of the stomach, which made him short of breath," and frequent attacks of vomiting and diarrhœa. About a week ago he began to have severe occipital and frontal headaches. For four months his feet have been slightly swollen, and for several months he has had a dry cough.

Physical Examination. An emaciated man of small stature, looking ten to fifteen years older than his correct age. There is a marked general pallor of the skin and mucous membranes, with a slight yellow-lemon hue. There are no hemorrhagic areas visible. The throat looks normal except the tonsils, which are a little reddened and swollen. There is no stomatitis. The muscles are small and flabby, and there is very little adipose tissue. Pulse, 100; temperature, 99°; respirations, 24.

Thorax. This is rounded and thickened anteroposteriorly. Its lower portion is bulged forward, forming a well-marked Harrison's groove on both sides. Lungs normal. The heart is either enlarged or displaced upward. The dulness from the upper border extends to the second interspace; the right border to the right edge of the sternum. The apex beat is felt in the fourth space one inch to the left of the midclavicular line. The first sound at the apex is weak; the second aortic is slightly exaggerated.

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[1] This is a term which is very loosely used in the coal regions and covers almost anything in the way of chronic bronchitis, emphysema, myocarditis, chronic nephritis, phthisis, or even the general failure of old age.

The arteries are prominent and tortuous and markedly thickened. The pulse is full and firm. Tension is not raised (132 mm. in radial by Riva-Rocci).

Abdomen. The left costal margin is bulged forward more than the right, and there is a visible tumor in the left hypochondrium. On palpation this tumor is evidently the spleen. The spleen is stony, hard, and smooth; the edges are sharp and well defined, but no notches can be felt. At this time the mass is not painful or tender. The upper border of splenic dulness is at the sixth space in the anterior axillary line. The right edge is felt one inch from the median line, and the lower margin is on a level with the antero-superior spines. The liver is also considerably enlarged. The dulness of the upper border begins at the fourth rib in the mid-axillary line. The lower border can be felt about one inch above the level of the umbilicus. It is not especially hard or sharp. There are no prominent veins over the abdomen.

The *eye-grounds* are somewhat pale, and the vessels look a little soft and flabby. There are no retinal hemorrhages.

The *urine* is pale, slightly turbid; specific gravity 1017; a small amount of albumin is present, and also a few granular casts. There is no sugar.

A blood examination the day after admission shows hæmoglobin, 58 per cent.; red cells, 2,500,000; white cells, 692,000.

DIFFERENTIAL COUNT OF 500 LEUKOCYTES.

Large and small mononuclears	8.0 per cent.
Transitional cells	2.0 "
Polynuclear eosinophiles	4.0 "
Polynuclear neutrophiles	37.5 "
Myelocytes, eosinophiles	3.5 "
Myelocytes, neutrophiles	45.0 "

In this count there were found several nucleated red cells, several mast cells, but no megaloblasts.

History after Admission. Second day: Severe attack of epistaxis. Ceased spontaneously. Slight diarrhœa. Sleeps badly.

Third day: Diarrhœa relieved by opium and bismuth.

Sixth day: Diarrhœa very troublesome again. Put on increasing doses of Fowler's solution.

Ninth day: Diarrhœa persists in spite of medication.

Thirteenth day: Hæmoglobin, 56 per cent.; red cells, 2,100,000; white cells, 620,000.

Fourteenth day: Pain in abdomen during urination. No hæmaturia. Has been voiding thirty-six to forty-six ounces daily. During next three days a marked diminution of urine. Returned to usual quantity under citrate of lithium.

Twenty-second day: Fowler's solution discontinued as patient begins to show physiological effects. Marked coryza. Hæmoglobin, 54 per cent.; red cells, 3,010,000; white cells, 208,000. The spleen is considerably diminished in size. It is three inches below costal border, and seems softer. Liver also diminished in size.

Twenty-fourth day: Fowler's solution recommenced. Another attack of epistaxis.

Twenty-eighth day: Has had sore throat for several days. Throat congested, but no hemorrhagic areas. Now has severe pain in left ear, and slight deafness. No tenderness over mastoid. Arsenic again has to be stopped.

Thirty-first day: Still sleeps badly. Weight, 103 pounds. Spleen still smaller. Lower border only one inch below ribs. Liver also smaller. Apex beat of heart is now in fifth space. Drum membrane has ruptured, and there is a profuse bloody discharge from the left ear. Hæmoglobin, 60 per cent.; red cells, 2,971,000; white cells, 44,300.

Thirty-third day: Left ear drum punctured by Dr. Murray. This was followed for six days by such profuse bleeding that canal had to be tamponed. Puncture relieved pain, but deafness is steadily increasing. An organic iron preparation given.

Thirty-seventh day: Fowler's solution, gtt. xv, t. i. d., again begun.

Fortieth day: Has been constipated. Weight, 103½ pounds. Specific gravity of blood, 1041; hæmoglobin, 62 per cent.; red cells, 3,430,000; white cells, 22,000.

Forty-fifth day: Weight, 105¾ pounds. Spleen and liver still felt about one inch below ribs.

Fifty-second day: Weight, 109½ pounds. Fowler's solution increased 1 gtt. daily.

Fifty-ninth day: Hæmoglobin, 50 per cent.; red cells, 2,260,000; white cells, 54,000. Deafness increasing in both ears. Has been up about ward, but now returned to bed on account of weakness. Spleen a little larger. Is two inches below ribs, and liver three inches. Weight, 110 pounds.

Sixty-fourth day: Has been eating very little, and yesterday and to-day has vomited frequently. First elevation of temperature since admission. Highest is 102° at 8 P.M. Next day 102.4° in evening. Evening temperature continued like this until death.

Sixty-fifth day: General abdominal pain for first time. No tenderness.

Sixty-eighth day: Diarrhœa again troublesome. Fowler's reduced to gtt. xviii, t. i. d.

Seventieth day: *x*-ray over spleen for eight minutes; five ampères; distance, nine inches. Diarrhœa checked with opium.

Seventy-second day: *x*-ray over spleen for twelve minutes; six ampères; distance six inches.

Seventy-third day: Fowler's solution reduced to gtt. x, t. i. d. Strychnine, gr. $\frac{1}{40}$, every four hours. *x*-ray to spleen for nine minutes; five ampères; distance seven inches.

DIFFERENTIAL COUNT OF 500 LEUKOCYTES.

Large and small mononuclears	9.0	per cent.
Transitional cells	5.0	"
Polynuclear eosinophiles	0.5	"
Polynuclear neutrophiles	22.0	"
Myelocytes, eosinophiles	0.5	"
Myelocytes, neutrophiles	63.0	"

During this count one megaloblast, seven normoblasts, and a few poikilocytes were found. Myelocytes are not uniform in size, many being much smaller than at the first count. Many of their nuclei stain faintly and show signs of degeneration. A few mast-cells present.

Seventy-fourth day: Eyelids reddened and complains of photophobia. Deafness is now complete. Complains of severe pains over liver and spleen, and attributes this to the x-ray. Patient says he can "feel the x-ray working" during treatment. x-ray discontinued on account of patient's weakness, which is progressing rapidly.

Hæmoglobin, 32 per cent.; red cells, 1,920,000; white cells, 7000 (!). (Count verified).

Seventy-fifth day: Very restless; complains of severe abdominal pain. Respirations very labored. Dulness, harsh breathing, and moist rales over both lungs behind. Coma about noon, and death at 6.30 P.M.

Autopsy Fifteen Hours after Death. Rigor mortis slight; postmortem lividity in dependent parts. Emaciation marked. Abdomen prominent.

Left Lung. Pleural cavity dry. A few slight adhesions at base. Deposits of coal-dust on parietal pleura. Lung weighs twenty-seven ounces. Crepitant all over except at base, where there is considerable hypostatic congestion. There is a marked general anthracosis. No tubercular scars.

Right Lung. Pleural cavity dry. There are a few slight adhesions at both apex and base. Anthracotic deposits on parietal pleura. Lung weighs thirty-one ounces. Pleura at apex is slightly contracted, but there are no definite signs of tuberculosis in the lung substance. Hypostatic congestion at base, but less marked than on left side. Same condition of anthracosis.

The *bronchial glands* and the glands around the lower part of the trachea are markedly anthracotic.

Heart. Pericardium is normal. Contains about one ounce of clear fluid. Heart weighs ten ounces. Muscle tissue pale. A small chicken-fat clot in left ventricle. Aortic and mitral valves are normal. No atheroma of arch of aorta. Papillary muscle pale. No zebra stripes. Ventricular wall of normal thickness. Chicken-fat clot in left ventricle. Pulmonic and tricuspid valves normal.

Spleen. Very dense adhesions to diaphragmatic peritoneum and to intestines. Weight, 52 ounces. Longest diameter, 21 cm. The cut surface is very firm, dark-red connective tissue, trabeculæ stand out prominently; the Malpighian bodies are not distinct. There is an old infarct at the upper pole, two inches in diameter on the surface; it is evidently undergoing fatty changes. The splenic pulp surrounding this infarct is markedly hemorrhagic. There are also numerous hemorrhagic spots in other portions of the spleen. In the lower part of the organ there are two other smaller infarcts.

Liver. Weight, 77 ounces. Color pale and waxy-looking. There is slight retraction of the cut edges of the capsule. Moderate degree of chronic congestion.

The general *peritoneum* is normal. Foramen of Winslow patent. The gall-bladder, urinary bladder, and pancreas are normal. There are several anthracotic glands around the head of the pancreas. There are no anthracotic glands in the lesser omentum. The mesenteric and retroperitoneal glands are not enlarged.

Alimentary Canal. There is marked chronic congestion of the mucous coat of the stomach, with considerable post-mortem digestion. There is also a marked congestion of the upper half of the small intestine. Large intestine is normal. Appendix normal, directed down and in toward pelvis. No trace of Meckel's diverticulum. No intestinal parasites.

Kidneys. Both similar. Weight, 5 ounces each. Capsule strips easily. Cut surface is rather pale. Cortex of normal thickness, and markings fairly distinct.

Prostate of normal size.

The *bone-marrow* of the ribs is dark red and does not present other unusual features. The marrow of the humerus is deep red, firm, and stands out prominently from the broken ends.

Microscopic Examination. (Tissues fixed in formalin and alcohol.)

Liver. There is some slight increase in the connective tissue. The liver parenchyma cells are fairly normal. They do not show fatty degeneration. The frequently described deposits of white blood cells are numerous. They are most prominent around the central veins and seem to consist principally of mononuclear cells and myelocytes. The central veins are generally empty, but many of the smaller arterioles seem to be plugged with leukocytes. There are a few small areas of extravasated blood among the liver cells in which the leukocytes are numerous. The capillaries of the liver are not dilated.

Lungs. These show the usual changes from anthracosis which are common in those who have worked a long time in coal mines. There is a considerable deposit of coal-dust in the walls of the air vesicles, in the connective-tissue septa, under the pleura, and around the bronchi and bloodvessels. There is some thickening of the walls of the air vesicles, and there is an increase of connective tissue around the larger deposits of dust. There is but little swelling and desquamation of epithelial cells, as is sometimes seen in those who have worked in the mines up to a few days of their death. There is no sign of a tubercular inflammation. The alveolar capillaries are not distended. At the bases of the lungs there is the ordinary picture of hypostatic congestion. In some places where there is an increase of connective tissue due to the anthracosis there are large deposits of leukocytes.

Heart Muscle. This shows quite a marked degree of fibrous myocarditis. The muscle cells are separated in many places by large patches of fine, poorly staining fibrillar connective tissue, with a few spindle-shaped nuclei. There are no deposits of white cells in the sections examined.

Pancreas. Normal.

Kidneys. These are but little changed. No special increase in the connective tissue. The glomeruli are normal. There is some swelling and cloudiness of the cells of the secreting tubules. No deposits of leukocytes are seen.

Alimentary Canal. Sections from the portions of the stomach saved show but little mucous membrane. The subserous and muscular coats are normal. Sections from the small intestine are normal.

Lymph Glands. The only glands preserved for cutting were those around the trachea. In these the deposit of coal-dust is so great that the fine structure is entirely obscured.

Spleen. (Stains by eosin and Delafield's hæmatoxylin, picro-acid fuchsin, carmine, borax, eosin, and methylene blue.) Sections from the infarct show no splenic tissue, but only dense fibrous connective tissue, with a few poorly formed bloodvessels. Surrounding the infarct in the splenic tissue there is a diffuse infiltration of old, much degenerated, blood. Throughout the splenic tissue proper the most marked change is an enormous increase in the normal connective tissue. This is represented both by an increase in size of the trabeculæ and by an increase in the intercellular reticulum. The Malpighian bodies are nowhere well formed and prominent. Throughout the splenic pulp there is a considerable infiltration of blood cells, which are in some places much degenerated; in others they are comparatively fresh. In the pulp the predominating cell is, of course, the small round lymphoid cell. In the blood cells extravasated in the splenic pulp there are a larger number of normoblasts and also more megaloblasts apparently than were seen in the smears during life. There are also many cells resembling the myelocytes, but considerably changed by the hardening process. A few of these latter show distinct mytotic figures. This was not noted in the blood during life. In a prolonged examination of the sections one polynuclear eosinophile leukocyte was seen. As usual in miners, there are many fine coal-dust particles scattered diffusely throughout the intercellular spaces of the spleen.

Bone-marrow. Smears from the ribs and humerus taken at the autopsy and stained by the blood methods show the same elements as the circulating blood, except that the normoblasts and megaloblasts are much more numerous. There are a few eosinophiles. Pieces of the ribs and humerus were decalcified in 5 per cent. nitric acid, hardened in alcohol, and stained by the same methods as the spleen. These sections show more marked changes from the normal than any other tissue examined. There are no fat or large "marrow" cells, and the whole appearance closely resembles that of well-formed granulation tissue. There is a fine connective-tissue reticulum, in the meshes of which there are cells which vary much in morphology and staining properties. Most of these cells are round and somewhat larger than a red cell. Their protoplasm is homogeneous, and takes the eosin faintly. They have a quite small, round, homogeneous nucleus. There is another, less frequent type of cell, which is larger, oval, granular, stains deeply with eosin, and has a large granular oval nucleus. There are a few very large cells resembling myelocytes, but it is difficult to trace much resemblance between the cells previously found in the circulating blood and those in the marrow sections after treatment by nitric acid and alcohol.

The Blood Picture. There is little to note in the red cells. They stain well; there is no polychromatophilia. Poikylocytes and normoblasts were noted, especially toward the last of the disease, and were not very numerous at any time. Megaloblasts were also present in small numbers. These were about three times the size of an ordinary red cell, and, while the nucleus was sometimes irregular, none showed definite mitosis.

The myelocytes which predominated were quite characteristic in type. As the total number of leukocytes diminished the morphology of these cells also changed. Many were much reduced in size, the nuclei stained faintly, and the granules became less prominent. The eosinophile myelocytes were also characteristic. These gradually fell in number from 3.5 per cent. to 0.5 per cent. of all leukocytes. And in the last slide examined none were found. The polynuclear eosinophile leukocytes, which at first showed a relative increase, also diminished, and finally disappeared as the disease progressed to its termination.

The accompanying chart graphically shows the course of the blood changes as determined by weekly counts.

Among the points of interest in this case are:

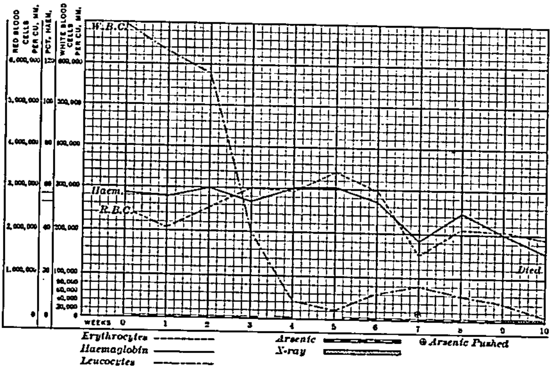
1. The fact that the man performed the active duties of an inside mine foreman for certainly two and probably six years after his disease began, and that he continued work up to ten weeks before the fatal termination.

2. The high leukocyte count of 692,000. We have not made an exhaustive search of the literature on this point, but among some

forty recent cases in easily available journals there was not given a higher count in chronic cases. An acute case of Hamman[1] and another quoted by him gave 958,000 and 790,000, respectively. While in exceptional cases the white may equal or exceed the red cells, our proportion of 1 : 3.6 is much above the average.

3. The disappearance of the previously increased eosinophiles. This fact, taken with Simon's case noted below, would tend to show that an increase in the number of eosinophiles is not so important a feature of this disease as has been considered.

4. An interesting symptom in this case was the deafness, which began in the fourth week of his stay in the hospital, and finally became complete. Deafness, while mentioned as a symptom in text-books—*e. g.*, Osler—is not spoken of in any case we have reviewed, except that of Mott.[2] Mott attributed its presence in his case to hemorrhage into the middle ear. That this is the true cause is well demonstrated in our case, as a hemorrhage actually did occur and spontaneously perforated the membrane. Bleeding was profuse for several days.



5. The great prominence of intestinal symptoms throughout the disease, suggesting autointoxication from the intestinal tract as a possible cause.

The most interesting questions arising in the study of leukæmia are connected with its etiology and with the relation of the different forms to each other.

During the last few years the infectious theory of its origin seems to be rapidly gaining ground. The acute leukæmias certainly seem to be infectious in origin, and the frequency of pharyngeal and tonsillar inflammation as a mode of onset cannot be ignored. The acute form of the disease, aside from its origin, frequently shows a decidedly septic type. Fussell, Jopson, and Taylor[3] noted this in thirty-one out of fifty-six acute cases which they collected.

Vehsemeyer placed leukæmias among autointoxications from the intestinal tract. As noted above, our own case suggests this, as diarrhœa was a prominent symptom throughout, especially at each exacerbation of the disease. During one of these, while under Dr. Thompson's care, he improved under small doses of calomel continued daily. Some of the exacerbations seem to have been relieved simply by a selected diet.

Simon's[4] case had recurring attacks of dysentery for twelve years before the apparent onset of the leukæmia. Diarrhœa was also a marked symptom in the previous history of Jewett's[5] case and of Miller's[6] case.

The much-quoted case of Obrastow, in which an attendant on a case of leukæmia also developed the disease in a few weeks, and one of Jewett's cases, in which a brother and sister seem to have had leukæmia, also point to an infectious disease. These cases in themselves are not, of course, conclusive.

Chmelar[7] fairly sums up the present status of the question when he says of leukæmia: "It has no specific cause, but arises under the influence of various acute and chronic infectious diseases, which alter and lead to excessive proliferation of the lymphoid elements." It does not seem that there is any connection between leukæmia and coal-mining, as this is the only case in a miner found in the last five years in the board of health records of Scranton, which has the largest coal-mining population in the United States.

The trend of opinion on the other point of the disease most under discussion—*i. e.*, the relation between the different clinical forms of leukæmia—seems to be toward the view that there is no specific difference between lymphatic and myelogenous leukæmia, but that they both are closely allied forms of fundamentally the same pathological condition. It would seem that the former sharp differentiation from the blood picture alone is little more than symptomatological. Indeed, if the hæmatologists are to make the classifications they will have to assume another form to include Simon's case of the myelogenous type without eosinophile cells. It would, perhaps, be as logical to consider tuberculous peritonitis with serous diffusion a specifically different morbid entity from the same disease with fibrin and adhesions.

The evidence as to fundamental unity of the two forms has now become a fairly logical chain, and is well summed up by Reed.[8] There seems little doubt now but that the acute and chronic forms are different only in the clinical course. While the acute type is generally the lymphatic, the myelogenous form does occur, as shown by the cases of Hirschfield and Cabot.

The first step in the evidence of the real identity of the two forms came in 1870 from Neuman. He showed that in each form the changes in the bone-marrow are marked. Reed's case, among others, seems, as she says, "to prove conclusively that we have here a lymphocytosis arising from proliferation of cells in the bone-marrow, and death occurring before any other organs showed involvement."

The establishment, too, of a mixed form of the disease further tends to show the close fundamental relation between the forms of leukæmia, and it seems that we will ultimately have to accept Reed's conclusion that "there are three forms of leukæmia, all due to myelogenous changes, and that they should be known as myelocytic, lymphoid, and mixed varieties, if we wish to make the blood picture the basis for clinical divisions."

The treatment of the disease is also an interesting feature. The value of arsenic, while real, is seldom more than temporary, though Simon and Campbell[9] report one case in which for a year the splenic tumor has been absent and the number of leukocytes normal. The authors believe that this is the only case on record showing this long-continued improvement. In our own case, as stated above, the disease was apparently held in check for probably six years by courses of arsenic.

The *x*-ray treatment is very promising, but its permanence cannot at this date be said to be proven. Heinke's[10] experimental work seems to show that the rays have a definite selective action, causing changes of a retrograde character in the spleen and lymphatic glands. From our present idea of the disease, however, this would apparently be attacking only a secondary result. Its curative action on the bone-marrow has yet to be demonstrated.

In our own case nothing can be inferred from the marked fall in leukocytes shortly after commencing the use of the rays, as the change may have been an ante-mortem one.

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